

WORKING P A P E R

A Technical Supplement: Estimating the Health Impact of New Antenatal Syphilis Screening Diagnostics in Africa

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PREFACE

This working paper contains technical material supporting the article by Aledort et. al. “Reducing the burden of sexually transmitted infections in resource-limited settings: the role of improved diagnostics.” *Nature*. S1 59-72 (2006). It is intended to be read in conjunction with that article. This supplement includes additional material referred to in the published article. Although this technical supplement in its current form has not been formally peer-reviewed, an earlier version of this paper, which also contained material that appears in the corresponding *Nature* paper, was reviewed by an outside expert and was revised in response to the reviewer’s comments.

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A. OVERVIEW

Syphilis is a significant cause of adverse pregnancy outcomes (including spontaneous abortion, stillbirth, intrauterine growth retardation, premature delivery and perinatal deaths) as well as congenital disease in infected infants and children⁴. Syphilis and its sequelae can be successfully managed, and the latter prevented, if infected mothers are diagnosed and treated appropriately by the middle of the second trimester^{4,5}. However, current options for the effective screening and serodiagnosis of syphilis infections in pregnant women require laboratory equipment, refrigeration, and trained personnel to perform and interpret the results, all of which are often unavailable in low-resource areas. Therefore, these tests rarely guide patient therapy in the developing world^{5,18,19}

We developed a model to quantify the potential health benefits of a new syphilis screening diagnostic for antenatal women to reduce syphilis-attributable mortality and morbidity in infants in sub-Saharan Africa, where the disease burden is particularly high.

A.1. SELECTION OF PRIORITY INTERVENTION POINTS FOR IMPROVED ANTENATAL SYPHILIS DIAGNOSTICS

Since the primary goal of a new diagnostic for syphilis is to reduce syphilis-related mortality and morbidity, the HIV/STI Expert Panel focused on particularly-affected populations, including pregnant women and their infants and high-risk transmitters, e.g., commercial sex workers (CSWs). There was immediate consensus that any new diagnostic for syphilis must be able to definitively distinguish active (i.e., untreated) from past (i.e., treated) infection in endemic settings, and three separate analyses were initially proposed, reflecting the relative contribution to disease burden by different populations: (1) syphilis screening in pregnant women who attend antenatal clinics (ANC); (2) syphilis screening in high-risk women who attend sexually transmitted disease (STD) clinics, and; (3) syphilis screening among infants.

RAND surveyed the experts in mid-April 2005 to narrow the scope of the group’s overall modeling efforts. Of the three syphilis analyses identified by the group, the low-risk model (i.e., antenatal syphilis screening) emerged as a clear priority due to the comparatively large burden of syphilis on infant mortality and morbidity in resource-poor settings. In addition, since antenatal screening resources are already in place in many resource-poor settings, pregnant women may be easier to identify and care for than high-risk women and infants. The experts agreed that the syphilis analysis should focus on sub-Saharan Africa, where syphilis disease burden among infants is thought to be greatest.

B. METHODS

B.1 Modeling Health Outcomes

To describe health outcomes, we defined four quantities denoted by TP , FP , FN and TN , to quantify the health outcomes that we attribute to a test result that is true positive, false positive, false negative and true negative respectively. The total health outcome is then computed as follows:

$$H = N_{tp} TP + N_{fp} FP + N_{fn} FN + N_{tn} TN$$

where N_{tp} , N_{fp} , N_{fn} , and N_{tn} are the number of women in each test outcome category.

We then considered several different health outcomes.

B.2. Stillbirths Due to Syphilis

To capture mortality associated with maternal syphilis, we calculated the number of stillbirths due to active syphilis. For women *without* active syphilis, we assumed no stillbirth risk, and we therefore set $FP = TN = 0$. Women who are false negatives remain untreated, and we assumed their fetuses experience a mortality risk equal to m_{fn} . The number of stillbirths for false negatives is therefore proportional to m_{fn} , and so we set

FN = m_{fn} . We assume that only a proportion p_{treat} of women who test positive receive effective treatment; the remaining fraction women $1 - p_{treat}$ who are true positive remain untreated and experience the same outcome as women who are false negatives. Treating active syphilis significantly reduces the risk of stillbirth, although the risk is still not 0, and we denote this risk by m_{tp} . Therefore the expected number of stillbirths for true positives is:

$$TP = p_{treat} m_{tp} + (1 - p_{treat}) m_{fn}$$

As a result, the total number of stillbirths due to active syphilis is expressed as follows:

$$D = p_{treat} N_{tp} m_{tp} + m_{fn} (N_{fn} + (1 - p_{treat}) N_{tp})$$

The risk of stillbirth for treated and untreated active syphilis and the probability of receiving effective treatment are reported in Table 1.

B.3. Risk of Stillbirths

In Watson-Jones¹ we find that risk of stillbirth for untreated women with active syphilis is 24.7%, while the risk of stillbirth for seronegative women is only 1.3%. Another study by Watson-Jones² found that the risk of stillbirth for women treated for active syphilis is 2.3%, while it is 2.5% in seronegative women. The latter study suggests that the risk of stillbirth for women with treated active syphilis and seronegative women is essentially the same. If this is the case, the first study implies that the risk of stillbirth for women with treated active syphilis is about 1.3%. Therefore we set the risk of stillbirth for true positives to $1.8\% = (2.3\% + 1.3\%)/2$.

The risk of stillbirth for false negatives found by Watson-Jones for Tanzania seems high (24.7%), since according to field experts historical rates suggested a risk of stillbirth of

10%. Therefore it is useful to derive an alternative estimate. We use the fact that the risk of stillbirth must be consistent with the high percentage of stillbirth attributable to syphilis (which we set to 49%, see above). Assuming that the risk of stillbirth for treated and seronegative women is the same, the following relationship must hold:

$$R^{untreated} / R^{treated} = (1 - p) / p \times \gamma / (1 - \gamma)$$

where $R^{untreated}$ and $R^{treated}$ are the risk of stillbirth among untreated and treated women with active syphilis, p is the prevalence of syphilis and λ is the fraction of stillbirths attributable to syphilis. If we believe the risk of 1.8% for the treated women, using a prevalence of 8% and a factor λ of 49% as estimated above, we find that $R^{untreated}$ must be 19.1%. Therefore we take the average of 24.7% and 19.1%, obtaining 21.9%, which is the number we will use.

B.4. Incorporating the Harm of Treatment

When a pregnant woman is treated for active syphilis (appropriately or inappropriately), with antibiotics, we assume that some harm to society follows. For example, sources of harm may include adverse events associated with treatment, and the development of antibiotic resistance. In the worst case scenario, if a pathogen develops resistance to an antibiotic agent, at some point in the future, individuals with a resistant strain of infection may not respond to treatment, thus causing future loss of life. In addition, once resistance occurs, new therapeutic agents must be developed, leading to additional costs, and consuming resources which may have been out to better use. In addition, each time we treat inappropriately with antibiotics we utilize scarce resources that may have been otherwise used to treat patients in need.

We quantify the harm of treatment with a single number C , which represents the fraction of lives lost, at some point in the future, as a result of treating one pregnant woman with antibiotics. The incremental health benefit of a new diagnostic compared to the status

quo, adjusted for this harm of treatment, is expressed in terms of the total number of lives *not* lost, or *saved*, or, ‘adjusted lives saved’. The total number of adjusted lives lost for both the status quo and the new diagnostic is computed as follows:

$$D_{\text{future}} = C(N_{tp} + N_{fp})$$

We estimated a range for C using the method described in Girosi et al.³ Conceptually, if a test for active syphilis is widely accepted and adopted by the medical community, then using the test must be better than the alternative of treating everybody or treating no one. We maintain that this is enough information to estimate approximately how much weight the medical community assigns to specificity relative to sensitivity. We then translate this revealed preference into an estimate for the harm of treatment C . The bound on C has the following form:

$$\frac{p(1 - \text{sens})(m_{fn} - m_{tp})}{p(1 - \text{sens}) + (1 - p)\text{spec}} \leq C \leq \frac{p\text{sens}(m_{fn} - m_{tp})}{p\text{sens} + (1 - p)(1 - \text{spec})}$$

where p is the prevalence of active syphilis in our population of interest, sens and spec are the sensitivity and specificity of the test being used, and m_{tp} and m_{fn} are the stillbirth rates for treated and untreated active syphilis. The bounds above are most informative when the test characteristics are poor. In other words, while it is always preferable to use a test that is perfectly sensitive and specific, this preference does not reveal much about the relative harm of treatment. The HIV/STI Expert Panel agreed that the Lab-based RPR test for active syphilis can have a specificity as low as 40% (because the status quo test does not differentiate well between active and inactive syphilis) and still be acceptable. That is, clinicians are willing to use a test it despite its high false positive rate for active syphilis because of the importance of detecting and treating true positive cases. Therefore, for the purpose of the bound above, we use a sensitivity of 85% and a specificity of 40%. This leads to the following bounds on C :

$$0.0028 \leq C \leq 0.01$$

To interpret these bounds, recall that each time we treat one pregnant woman for active syphilis, C future lives are lost, or, for every $1/C$ pregnant woman treated, one future death is incurred. Therefore, if C is 0.0028, for every 357 pregnant women treated for active syphilis, one future life is lost. Similarly, if C is 0.01, for every 100 pregnant women treated, we lose one life. The method described in Appendix C does not tell us how to choose a value of C within the bounds. Our panel of experts agreed that the lower bound was a much more credible estimate of C than the upper bound, given current practice, so we set C equal to 0.0028 and varied it extensively in sensitivity analysis.

B.5. Cases of Congenital Syphilis

To account for the significant morbidity associated with syphilis, we also considered the number of congenital syphilis cases as an outcome. Specifically, children born with congenital syphilis experience lifetime disabilities. If so desired, this outcome can be converted to disability-adjusted life years (DALYs) by attaching an appropriate DALY weight and duration to the outcome. The computation of the number of cases of congenital syphilis is relatively straightforward. We assumed that the risk of congenital syphilis for infants born to *treated* women was negligible, and we therefore set $TP=TN=FP=0$. Denoting p_{cs} the risk of congenital syphilis among *untreated* cases, we set $FN = (1 - m_{fn})p_{cs}$, and the total number of cases as:

$$D_{cs} = N_{fn} (1 - m_{fn}) p_{cs}$$

C. ADDITIONAL MODEL LIMITATIONS

We made some simplifying assumptions about the course of infection in pregnant women. Specifically, we assume that *active syphilis* refers to a maternal syphilis infection that a woman may pass on to her infant, and which requires treatment with antibiotics. To this end, we did not incorporate the effect of diagnosis on *stage* of infection, i.e., primary versus secondary. Furthermore, we assume that syphilis is present

at the beginning of the pregnancy, and we therefore discount the small proportion of women who may acquire syphilis during pregnancy. Although treatment may in fact be somewhat less effective when administered late in pregnancy versus earlier in pregnancy e.g., to prevent congenital syphilis, the proportion of pregnant women who present to a clinic for the first time in the 3rd trimester and the effectiveness of treatment later in a pregnancy have not been well described. We therefore did not explore the effect of the timing of treatment on health outcomes and instead assumed that women who test positive and are treated receive antibiotic treatment at the optimal time in their pregnancy (i.e. early 2nd trimester), and that treatment is perfectly effective.

D. ADDITIONAL MODEL CALIBRATION DETAILS

Prior to evaluating the potential impact of a new antenatal syphilis screening test, we explored the predictive validity of the model by calibrating the model outcomes to exogenous estimates of stillbirth deaths. To do this, we estimated the number of syphilis-attributable stillbirths by multiplying the number of reported stillbirths in sub Saharan Africa. by the proportion of stillbirths attributable to syphilis.⁴

D.1. Stillbirth Rate

In a recent document, the WHO reports neonatal and perinatal mortality estimates at country and regional level.⁵ The estimates are given for year 2000; more recent estimates are not available. The stillbirth rate for sub-Saharan Africa is derived by aggregating the stillbirth rates for all Africa, excluding Northern Africa. The resulting stillbirth rate for the region is 3.4%. We confirmed this result by aggregating the country level stillbirth rates found in the World Health Report 2005,⁶ and we found perfect agreement.

Note that the stillbirth rate must satisfy the following relationship:

$$SBR = p \times m_{FN} + (1 - p) \times m_{TN}$$

where p is the prevalence of syphilis.

D.2. Proportion and Number of Stillbirths Attributable to Syphilis

We then estimated the number of stillbirths attributable to syphilis. Although the proportion of syphilis-attributable stillbirths is not well defined in the literature, in Tanzania, Watson-Jones and colleagues found that 51% of stillbirths are attributable to syphilis¹. And in Zambia, Ratnam et al. set this number to 42%⁷. Weighting these figures by the number of births, we set the fraction of stillbirths due to syphilis to 49%. To estimate the *number* of stillbirths due to syphilis, we then multiplied this estimated proportion by our target population of pregnant women. We used births as a proxy for the number of pregnant women, estimating the number of births in 2006 from the medium variant of the projection for the period 2005-2010 provided by the UN Population Division.⁸ We applied the proportion of 49% to our population of about 31 million pregnant women and obtained an estimate of about 210,000 stillbirths attributable to syphilis.

Using the parameters of Table 1 in Aledort et al.⁹, our status quo model predicted close to 230,000 stillbirths, only 10% more than the estimated actual number based on the methods described above. This suggests that the estimates generate outcomes for the status quo model that are generally consistent with external data.

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